REMARKS

Courtesies extended by the Examiner and his supervisor, Terry McElvey, during a telephone interview conducted on December 20, 2001 to discuss allowable subject matter are gratefully acknowledged. New claims 40-68 presented by this communication are intended to reflect the subject matter outlined by the Examiner as allowable during the interview.

Claims 1-3, 5, 7-14, 16-24, and 26-39 were pending before this response. By the present communication, claims 1-3, 5, 7-14, 16-24, and 26-39 are canceled without prejudice and new claims 40-68 are presented to define Applicant's invention with greater particularity. No new matter has been added as the new claim language is fully supported by the specification and original claims. Applicant submits that the claim amendments do not narrow the claims in any way within the meaning of Festo Corporation v. Shoketsu Kinzoku Kogyo Kabushiki Co. Ltd., a/k/a SMC Corporation and SMC Pneumatics, Inc., 234 F.3d 558, 51 U.S.P.Q. 2d 1959 (Fed. Cir. 2000). Accordingly, claims 40-68 are currently pending and under consideration as shown in attached Exhibit A.

The Specification

The title of the invention is amended to more accurately reflect the subject matter of the new claims presented herein.

The Declaration

The Office Action asserts that the declaration under 37 C.F.R. § 1.132 filed April 26, 2001 is insufficient to overcome the rejection of claims 1-3, 5, 7-14, 16-24 and 26-39 based upon an alleged lack of enabling disclosure under 35 U.S.C. § 112, First Paragraph, because the Declaration submitted was not signed. An additional copy of the Supplementary Declaration under § 1.132, which was signed by the inventor Matthias G. Von Herrath on April 29, 2001, is submitted herewith as Exhibit B (hereinafter referred to as "the Exhibit B Declaration").

Applicants respectfully submit that this signed copy of the Exhibit B Declaration meets all requirements under 37 C.F.R § 1.132.

Claim Objections

Claims 8 and 29 are object to for allegedly containing informalities. By the present communication claims 8 and 29 have been cancelled. Therefore, Applicants respectfully request reconsideration and withdrawal of the objection to claims 8 and 29 as allegedly containing informalities.

The Rejection under 35 U.S.C. § 112, First Paragraph

Applicant respectfully traverses the rejection of claims 1-3, 5, 7-14, 16-24 and 26-29 under 35 U.S.C. § 112, First Paragraph, for alleged lack of an enabling disclosure. Claims 1-3, 5, 7-14, 16-24 and 26-29 are cancelled without prejudice. Applicant respectfully submits that the Examiner's assertion that the specification does not reasonably provide enablement for treatment of any autoimmune disorder, such as diabetes, does not apply to the subject matter of new claims 40-68.

In particular, Applicant disagrees with the Examiner's assertion that "Giannoukakis et al. have taught the unpredictability *of the claimed invention*" (Office Action, page 5, emphasis added). In fact, Giannoukakis' assertions regarding the safety risks and unpredictability pertain to therapeutic treatments of diabetes wherein foreign islet producing cells (for example, porcine cells or cell obtained from cadavers) are introduced into the subject, but do not, therefore, apply to the invention as set forth in new claims 40-68. Giannoukakis' method of transplanting insulin-producing cells depends for utility upon *in vivo* viability and continued function of transplanted cells in the subject's body (i.e., to produce a therapeutic amount of insulin). Because the cells are foreign, the subject's host inflammatory response tends to destroy the transplanted cells and may attack healthy islet cells as well.

Alternatively, in the embodiments of Giannoukakis' method wherein DNA is administered to a subject, the method utilizes a gene therapy-like application, wherein efficacy of the treatment requires that the gene product be expressed in the subject over an extended period of time and at substantial levels to supplement a lack of insulin. Thus, in all cases the treatment is successful only so long as the administered construct produces a therapeutic drug *in vivo* in the subject. Applicants respectfully submit that "no showing of any previous success" by Giannoukakis, as asserted by the Examiner, does not necessarily predict constant lack of success in future scientific attempts, particularly when different methods and strategies are employed.

Applicant has submitted two Declarations under 37 C.F.R. §1.132 that provide proof that the invention methods and strategies, which differ considerably from those employed by Giannoukakis provides verifiable positive results in treatment of autoimmune diabetes. In Applicant's methods for "treating a condition associated with autoimmune diabetes" (claim 47), for "treating autoimmune diabetes" (claim 54), and for "treating an autoimmune process associated with autoimmune diabetes" (claim 62), plasmids containing nucleic acid encoding insulin B chain and/or GAD and IL-4 and/or IL-10 are expressed in the subject. Those of skill in the art recognized that insulin B chain and GAD are self-antigens both in type 1 diabetes in humans and in spontaneous animal models.

In the first § 132 Declaration under 37 C.F.R. § 1.132 (filed on December 28, 2000), Applicant describes experiments utilizing two complementary mouse models of autoimmune diabetes. In the first, the RIP-LCMV model, the disease is triggered by viral infection and mediated by molecular mimicry. Thus, this is an "environmental" model. The second model is a spontaneous disease model, the NOD mouse model, based on segregation of a number of diabetes-associated genes that predispose to disease irrespective of environmental factors. Since the human disease is triggered by interplay of genetic and environmental factors, these models represent the two mechanisms operative in human autoimmune diabetes. Applicant respectfully

submits that this demonstration that plasmid-mediated expression of insulin B is effective in *both* models would be considered by those of skill in the art to be predictive for human outcomes.

As described in the §132 Declaration submitted herein, in the first experiment, tests were conducted to determine the effect of induced peripheral expression of self-antigen (porcine insulin B chain) (InsB) on spontaneous occurrence of IDDM in *nod* mice in which diabetes occurs spontaneously in 80% of the females and 30% of the males by 30 weeks of age. The mice were administered intramuscularly a plasmid engineered to express porcine insulin B chain DNA under the control of the initial-early promoter of CMV at the age of 7 days, with boosting at 4 and 8 weeks. Only around 35% of the treated mice displayed full-blown disease in contrast with the expected rate of 80% in naïve female *nod* mice.

As further described in the § 132 Declaration, intramuscular administration of the plasmid to *nod*-mice resulted in long-lasting expansion of *both GAD and InsB-specific T cell pool* committed toward IL-4, but not IFN-γ production (Fig. 2), as shown in the spleens of diabetes-free 30-weeks old treated mice. Thus, a regulatory immune response resulted in treated mice for an epitope (i.e., GAD) that is associated in humans with autoimmune diabetes, but was not included in the plasmid administered.

In addition, an ELISA-based analysis of the effect upon the autoreactive T cell repertoire in mice administered the InsB-containing plasmid that did not develop diabetes by 30 weeks of age showed (Table 2 of Declaration) increased production of IL-4 and TGF-β1 by infiltrating T cells as compared to naïve or control plasmid-inoculated mice. Furthermore, the infiltrating T cells from pInsB-vaccinated mice displayed reduced production of IL-1β. According to the Declaration of Dr. von Herrath, this cytokine profile indicates that in protected mice that were treated according to invention methods a modified autoreactive T cell profile was triggered consisting in a shift from Th1 to Th2 immunity. This study illustrates efficacy of the invention compositions and methods for treating an autoimmune process associated with autoimmune diabetes.

To further address the Examiner's concern raised in the Advisory Action that "only IL-4 would provide any benefit in the claimed method," Applicant submitted an unexecuted Supplementary Declaration under 37 C.F.R. § 1.132 by the inventor, Dr. Von Herrath (an executed copy of which is attached hereto as Exhibit B). The Supplemental Declaration describes an additional experiment conducted in which *nod* female mice were injected with invention plasmids containing Ins B chain or with a combination of plasmids expressing Ins B and either IL-10 or IL-4. The results of these tests summarized in Figure 1 attached to the Supplemental Declaration (Exhibit C) show that the combination of Ins B and IL-10 transiently expressed in the treated mice was even more effective at reducing the percent cumulative rate of disease in immunized mice as measured by blood glucose levels in the treated mice than the combination of Ins B and IL-4. These studies illustrate efficacy of the invention compositions and methods for treating a condition associated with autoimmune diabetes.

In view of the amended language of new claims 40-68, the first § 1.132 Declaration filed on December 28, 2000, and the Supplemental Declaration submitted herewith (Exhibit B), Applicant submits that the present Specification provides sufficient objective data to fully enable the subject matter of new claims 40-68. Therefore, reconsideration and withdrawal of the present rejection for lack of enablement are respectfully requested.

The Rejection under 35 U.S.C. § 102(b)

Applicant respectfully traverses the rejection of claims 1, 2, 5 and 7-9 under 35 U.S.C. § 102(b) for allegedly being anticipated by WO 97/46253. The Examiner asserts that WO 97/46253 discloses an immunomodulating composition comprising a nucleic acid construct encoding at least one epitope from a self-antigen and a gene encoding a cytokine. However, claims 1, 2 5 and 7-9 are cancelled by the present communication. In addition, Applicant's invention immunomodulating compositions for use in treating a condition or autoimmune process associated with autoimmune diabetes, as defined by new claim 40, distinguish over the disclosure of WO 97/46253 by reciting a composition comprising "one or more nucleic acid

constructs encoding a self-antigen selected from GAD, insulin B-chain, and a combination thereof and a cytokine selected from IL-10, IL4, and a combination thereof, in a pharmaceutically acceptable carrier." WO 97/46253 is absolutely silent regarding a composition for treatment of autoimmune diabetes, much less the specific composition of Applicant's composition claims. Accordingly, Applicant respectfully submits that WO 97/46253 fails to disclose each and every element of the claims as would be required to establish anticipation under 35 U.S.C. § 102(b). Accordingly reconsideration and withdrawal of the rejection are respectfully requested.

The Rejection under 35 U.S.C § 103

Applicant respectfully traverses the rejection of claims 1-3, 5, 7-14, 16-24 and 26-39 as allegedly being unpatentable over Liu et al in view of WO 97/46253. Claims 1-3, 5, 7-14, 16-24 and 26-39 are cancelled.

In addition, Applicant respectfully submits that Jingxue Liu et al. (*Gene Ther Mol Biol* 3:197-206, 1998; hereinafter "Liu et al") is unavailable as a reference against the present invention, as defined by new claims 40-68. Applicant submits herewith a Declaration under 35 C.F.R. §1.131 (attached as Exhibit C) signed by the inventor Matthias G. von Herrath, stating that the claimed invention was conceived and reduced to actual practice under his direction while he was the leader of the research team that performed the experiments set forth in the Examples of the present application prior to the publication date in 1998 of Liu et al. This statement is supported by attached true copies (with dates redacted) of pages from The Scripps Research Institute Technology Disclosure document signed by Dr. von Herrath and an unpublished short manuscript entitled "DNA immunization to prevent autoimmune diabetes" that was prepared for publication in the technical journal *Nature Medicine* prior to the date of publication in 1998 of the Liu article.

Furthermore, the § 1.131 Declaration states that the co-authors Bryan Coon, Ling-Ling An, and J. Lindsay Whitton, named as co-authors of the article entitled "DNA immunization to prevent autoimmune diabetes," are not co-inventors of the present invention. These named co-authors contributed to the research effort described in the article, but are not co-inventors of the subject matter of the present invention, as defined by new claims 40-68, because they did not contribute to conception of the invention described in the subject article.

Therefore, Applicants respectfully submit that Liu et al is not available as a reference under 35 U.S.C. § 102(a) against the claims of the present application.

Moreover, Applicant respectfully submits that WO 97/46253 is insufficient alone to render obvious the subject matter of new claims 40-68. WO 97/46253 is absolutely silent regarding compositions and methods for treatment of autoimmune diabetes, much less the specific compositions of Applicant's invention, as defined by new claim 40, which are required to comprise "one or more nucleic acid constructs encoding a self-antigen selected from GAD, insulin B-chain, and a combination thereof and a cytokine selected from IL-10, IL4, and a combination thereof, in a pharmaceutically acceptable carrier." Similarly, WO 97/46253 is absolutely silent regarding any methods for treating autoimmune diabetes, much less the specific methods of Applicant's invention, as defined by new claims 47, 54 and 62, which require administering to the subject by peripheral administration an immunomodulatory effective amount of one or more plasmids expressing a nucleic acid construct encoding an antigen selected from insulin B chain, GAD, and a combination thereof and a cytokine selected from IL-4, IL-10, and a combination thereof, in a pharmaceutically acceptable carrier, wherein transient expression of the self-antigen and the cytokine in the subject treats the autoimmune diabetes, or condition or autoimmune process associated therewith Therefore, Applicant respectfully submits that WO 97/46253 is insufficient to establish *prima facie* obviousness of claims 40-68 under 35 U.S.C. § 103. Accordingly reconsideration and withdrawal of the rejection over the combined disclosures of Liu et al. and WO 97/46253 are respectfully requested.

Conclusion

In view of the Declarations submitted herewith and the above amendments and remarks, reconsideration and favorable action on new claims 40-68 are respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

Date: January 17, 2002

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Attachments: Exhibit A – Pending claims
Exhibit B - Executed copy of Supplementary Declaration under 37 C.F.R. § 1.132
Exhibit C - Declaration under 37 C.F.R. § 1.131

EXHIBIT A

Version with Markings to Show Changes Made

In the Specification:

Please delete the title of the Specification and insert the following replacement Specification title: COMPOSITIONS AND METHODS FOR THE TREATMENT OF AUTOIMMUNE DIABETES--.

In the Claims

Please cancel claims 1-3, 5, 7-14, 16-24, and 26-39 without prejudice.

Please enter the following new claims:

-- 40. (New) An immunomodulating composition for treating a condition or autoimmune process associated with autoimmune diabetes, said composition comprising one or more nucleic acid constructs encoding a self-antigen selected from GAD, insulin B-chain, and a combination thereof and a cytokine selected from IL-10, IL4, and a combination thereof, in a pharmaceutically acceptable carrier.

41. (New) The composition of claim 40, wherein the autoimmune diabetes is type I diabetes.

42. (New) The composition of claim 40, wherein the self-antigen is insulin B-chain.

43. (New) The composition of claim 40, wherein the self-antigen is GAD.

44. (New) The composition of claim 40, wherein the construct includes a plasmid.

45. (New) The composition of claim 40, wherein the nucleic acid construct further comprises a regulatory element operatively linked to nucleic acid encoding the self-antigen or the cytokine.

46. (New) The composition of claim 45, wherein the regulatory element is a promoter selected from the group consisting of Mouse Mammary Tumor Virus (MMTV) promoter, Human Immunodeficiency Virus Long Terminal Repeat (HIV LTR) promoter, Moloney virus, ALV, Cytomegalovirus (CMV) promoter, human Actin, human Myosin, RSV, human Hemoglobin, human muscle creatine and EBV.

47. (New) A method for treating a condition associated with autoimmune diabetes in a subject in need thereof comprising administering to the subject by peripheral administration an immunomodulatory effective amount of one or more plasmids expressing a nucleic acid construct encoding an antigen selected from insulin B chain, GAD, and a combination thereof and a cytokine selected from IL-4, IL-10, and a combination thereof, in a pharmaceutically acceptable carrier, wherein transient expression of the self-antigen and the cytokine in the subject treats the condition associated with the autoimmune diabetes.

48. (New) The method of claim 47, wherein the subject is a human.

49. (New) The method of claim 47, wherein the self-antigen is insulin B-chain.

50. (New) The method of claim 47, wherein the self-antigen is GAD.

51. (New) The method of claim 47, wherein the nucleic acid construct further comprises a regulatory element operatively linked to nucleic acid encoding the self-antigen or the cytokine.

52. (New) The method of claim 51, wherein the regulatory element is a promoter selected from the group consisting of Mouse Mammary Tumor Virus (MMTV) promoter, Human Immunodeficiency Virus Long Terminal Repeat (HIV LTR) promoter, Moloney virus, ALV, Cytomegalovirus (CMV) promoter, human Actin, human Myosin, RSV, human Hemoglobin, human muscle creatine and EBV.

53. (New) The method of claim 47, wherein the treatment comprises controlling the blood sugar of the subject.

54. (New) A method for treating autoimmune diabetes in a subject in need thereof comprising administering to the subject by peripheral administration an immunomodulatory effective amount of one or more plasmids expressing a nucleic acid construct encoding an antigen selected from insulin B chain, GAD, and a combination thereof and a cytokine selected from IL-4, IL-10, and a combination thereof, in a pharmaceutically acceptable carrier, wherein transient expression of the self-antigen and the cytokine in the subject treats the condition associated with the autoimmune diabetes.

55. (New) The method of claim 54, wherein the subject is a human.

56. (New) The method of claim 54, wherein the self-antigen is insulin B-chain.

57. (New) The method of claim 54, wherein the self-antigen is GAD.

58. (New) The method of claim 54, wherein the nucleic acid construct further comprises a regulatory element operatively linked to nucleic acid encoding the self-antigen or the cytokine.

59. (New) The method of claim 58, wherein the regulatory element is a promoter selected from the group consisting of Mouse Mammary Tumor Virus (MMTV) promoter, Human Immunodeficiency Virus Long Terminal Repeat (HIV LTR) promoter, Moloney virus, ALV, Cytomegalovirus (CMV) promoter, human Actin, human Myosin, RSV, human Hemoglobin, human muscle creatine and EBV.

60. (New) The method of claim 54, wherein the treatment comprises controlling the blood sugar of the subject.

61. (New) The method of claim 54, wherein the treatment comprises induction of T-cells reactive to the self-antigen.

52. (New) A method for treating an autoimmune process associated with autoimmune diabetes in a subject in need thereof comprising administering to the subject by peripheral administration an immunomodulatory effective amount of one or more plasmids expressing a nucleic acid construct encoding an antigen selected from insulin B chain, GAD, and a combination thereof and a cytokine selected from IL-4, IL-10, and a combination thereof, in a pharmaceutically acceptable carrier, wherein transient expression of the self-antigen and the cytokine in the subject treats the immune process associated with the autoimmune diabetes.

63. (New) The method of claim 62, wherein the subject is a human.

64. (New) The method of claim 62, wherein the self-antigen is insulin B-chain.

65. (New) The method of claim 62, wherein the self-antigen is GAD.

66. (New) The method of claim 62, wherein the nucleic acid construct further comprises a regulatory element operatively linked to nucleic acid encoding the self-antigen or the cytokine.

67. (New) The method of claim 66, wherein the regulatory element is a promoter selected from the group consisting of Mouse Mammary Tumor Virus (MMTV) promoter, Human Immunodeficiency Virus Long Terminal Repeat (HIV LTR) promoter, Moloney virus, ALV, Cytomegalovirus (CMV) promoter, human Actin, human Myosin, RSV, human Hemoglobin, human muscle creatine and EBV.

68. (New) The method of claim 62, wherein the treatment comprises induction of T-cells reactive to the self-antigen. --

EXHIBIT B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	M. Von Herrath	Art Unit:	1636
Application No.:	09/336,672	Examiner	W. Sandals
Filed:	June 17, 1999		
Title:	COMPOSITIONS AND METHODS FOR THE TREATMENT OR PREVENTION OF AUTOIMMUNE DISORDERS		

Commissioner of Patents
Washington, D.C. 20231

SUPPLEMENTAL DECLARATION OF APPLICANT UNDER 37 C.F.R. §1.132

Sir:

I, Matthias G. von Herrath, M.D., inventor of the above-identified application, do hereby declare and state that:

1. I am familiar with the content of the above-identified application, including the methods for modulating an ongoing immune response to a self-antigen associated with autoimmune diabetes contained in the Specification therein.

2. An experiment in addition to those described in my Declaration under 37 C.F.R. §1.132 signed on December 21, 2000 have been conducted under my supervision and control in the laboratories of The Scripps Research Institute, Department of Neuropharmacology, Division of Biology, in La Jolla, California, using the methods and procedures disclosed in the above-identified application to illustrate the efficacy of the invention methods for modulating an immune response against a self-antigen associated with autoimmune diabetes .

3. In this additional experiment, tests were conducted to determine the effect of induced peripheral expression of self-antigen (porcine insulin B chain) (InsB) on spontaneous occurrence of IDDM in *nod* mice. Mice used in the experiments were female *nod/scid* mice obtained from Jackson Laboratories or *nod* mice bred from *Nod*/LtJ breeders (Taconic Farms) in

which diabetes occurs spontaneously in 80% of the females and 30% of the males by 30 weeks of age.

The mice were vaccinated with a plasmid engineered to express porcine insulin B chain DNA (InsB) under the control of the initial-early promoter of CMV. The plasmid is commercially available, widely used and described previously by Coon et al., *J. Clin. Invest.*, 1999, 104:189; Yokoyama et al., *J. Virol.*, 1995, 69:2684. The IE-CMV promoter has previously been shown to support transcription of various antigens in mammalian cells. The plasmid was expanded and purified from *E. coli*, using the Quiagen method. Alternatively, the mice were administeted the InsB-expressing plasmid (pCMV-InsB) together with a plasmid expressing either IL-10 or IL-4 under the control of a HTLV promoter (respectively (pHTLV-IL-10 and pHTLV-IL-4). Immunizations were at the age of 7 days (gluteal muscle) with booster inoculations at 4 and 8 weeks (quadriceps muscle), bilaterally, at a total dose of 100 μg or 50 μg of the pCMV-Ins B + 50 μg of pHTLV-IL-4 or pHTLV-IL-10. in 100 μl of sterile PBS. Controls were naïve mice and mice administered pCMV plasmid without the interleukin The number of mice per group were as follows: naïve, (n=19); pCMV (n=13); pCMV-InsB (n=20), together with a plasmid expressing either IL-10 or IL-4 under the control of a HTLV promoter (respectively (pCMV-InsB + pHTLV-IL-10 (n=9); pCMV-InsB + pHTLV-IL-4 (n=10).

The blood glucose was monitored every two weeks beginning at 10 weeks of age. As shown in Figure 1 attached hereto as Exhibit 1, statistical analysis (p of log-rank test < 0.05) showed a significant suppression of increase in blood glucose levels in nod females immunized with plasmids encoding Ins-B or with a combination of plasmids encoding Ins-B and either IL-4 or IL-10.

Thus, this experiments show that administration to female *nod* mice of a plasmid containing DNA encoding bovine insulin B chain, optionally augmented by administration of a plasmid containing either IL-4 or IL-10, significantly suppressed an increase in blood glucose, a clinical symptom of autoimmune diabetes.

4. I further declare that all statements made herein of knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine, or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

4/29/01
Date

Matthias G. von Herrath, M.D.

Attachments
Figures 1.